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Comments:

The request from the Registration Division was for evaluation of studies other than short term ones submitted by Getty Refining and Marketing Company, March 22, 1983, Acc. No. 249909. For this reason certain acute studies (for which guidelines have been published) have not been reviewed. Each review has been identified not only by the accession number but also by the tab number as received. Additional reports will be reviewed if a request is made.

Only one submitted publication met the minimum requirements for suitability for our use in the registration process. This was the teratology study, Tab 14. The review is attached. Tab 38 is an addendum to this study.

Several other submitted publications have been reviewed for possible supplemental value and their reviews are also attached. These had tabs 15-6, 18-22, 28, 30 and 33-37.

No reviews were prepared for several publications because either the publications were themselves reviews without original data or the publications were so lacking in description of protocol or of results that they were not adequate for our use. Original reports are preferred. These included tabs 10, 13, 17, 29 and 32.

Tab 31 is illegible.

1

Toh N	LIST OF DOCUMENTS
Document	Title
1	Analytical Report (1982).
2	Rates of Microbial Transformation of Polycyclic
	Aromatic Hydrocarbons in Water and Sediments in the
•	Vicinity of a Coal-Coking Wastewater Discharge (1981).
3	The Decomposition of Naphthalene in the Soil and the
	Effect Upon Its Insecticidal Action (1928).
4	Acute Toxicity of Pesticides (1969).
5	Registry of Toxic Effects of Chemical Substances (1980).
. 6	Acute Toxicity, Inhalation Toxicity and Skin Irritation of
· ·	Cyclododecane, Tricyclododecane, Naphthalene and
	p-Dichlorobenzene (1973).
•7	Tests of the Acute Toxicity of Naphthalene (1980).
8	Naphthalene (1980).
9	Naphthalene (1980).
10	Naphthalene (1976).
11	Exfoliative Dermatitis Due to Naphthalene (1940).
12	Summary of Prechronic Studies (1980).
13 -	Bioassays of Naphthalene and Alkylnaphthalenes for
1 .	Co-carcinogenic Activity. Relation to Tobacco
	Carcinogenesis (1978).
14)	Testing of Selected Workplace Chemicals for Teratogenic
	Potential (1981).
15	Detection of Carcinogens as Mutagens in the Salmonella/
	Microsome Test: Assay of 300 Chemicals (1975).
16	Mutagenicity of 1,2-ring-fused Acenaphthenes against S. typhimurium

i(17)	S. typhimurium and E. coli to Detect Chemical Mutagens (1974).
(18)	Screening of Carcinogens with the Prophage clts857 Induction
	Test (1981).
(19)	Effect of Weak-, Non-, and Co-carcinogenic Chemicals on
•	2-Acetylaminofluorene-Induced Mutation in Salmonella Typhimurium (197
20	Transformation of Cultured Mouse Mammary Glands by Aromatic Amines
	and Amides and Their Derivatives (1979).
· (21)	Evaluation of an In Vitro Assay System for Carcinogens
	Based on Prior Infection of Rodent Cells with Nontransforming RNA
	Tumor Virus (1974).
(22)	Transformation of Cell Cultures as an Indication of the Carcinogenic
r	Potential of Chemicals (1973).
23	Aquatic Toxicity of Naphthalene (1980).
24 .	Reduced Growth of Coho Salmon Fry Exposed to Two Petrcleum Components,
	Toluene and Naphthalene, in Fresh Water (1981).
25	Effects of Temperature on the Median Tolerance Limit of Pink Salmon
•	and Shrimp Exposed to Toluene, Naphthalene, and Cook Inlet Crude
•	Oil (1979).
26 .	Other Aquatic Toxicity Data for Naphthalene (1980).
1 .27	The Chronic Toxicity to Daphnia Magna of Acridine, a Representative
	Azaarene Present in Synthetic Fossil Fuel Products and Waste Waters
	(1981).
(28)	A study of the Correlation between the Biochemical and Intra-ocular
- .	Changes Induced in Rabbits by the Administration of Naphthalene.
(29)	Genetic Differences in Cataract and Other Ocular Abnormalities Induced
	by Paracetamol and Naphthalene (1980).
	3
•	<u>.</u>

TA1537 and TA1538: Structure-Activity Relationships (1980).

<u> </u>	Alterazioni Oculari da Naftalina (1956).
31	Acute Hemolytic Anemia Due to Naphthalene Poisoning (1949).
(32)	Test for Hypersusceptibility to Hemolytic Chemicals (1963).
(33)	Acute Hemolysis Due to Naphthalene Inhalation (1963).
(34)	Cell Damage and Inhibition of Pulmonary Mixed-Function Oxidase
	Activity by Naphthalene (1981).
<u>3</u> 5	Morphology of a Naphthalene-Induced Bronchiolar Lesion (1977).
(36)	Carcinoma of the Larynx among Naphthalene Cleaners (1978).
(37)	Transplacental Naphthalene Poisoning (1957).
(38)	Data Summaries, NIOSH, Teratogenicity Study on Naphthalene.

Study Type: Teratology and fetal toxicity in rats.

Accession Number: 249909 (14)

Title: Testing of selected workplace chemicals for teratogenic potential.

Journal: Scand j work environ health 7 (1981): Suppl 4, 66-75.

Authors: Bryan D. Hardin, MS, Gary P. Bond, MS, Mr. Sikov, Ph.D., FD Andrew, Ph.D., Robert P. Beliles, Ph.D.,

Richard W. Niemeier, Ph.D.

Test material: Naphthalene.

Protocol:

Napthalene was one of 19 chemicals tested in this study. "10-15 inseminated female rats" were each given, by I.P. injection, 395 mg/kg (the MTD) of naphthalene in corn oil on days 1 through 15 of gestation. Corn oil was used as the negative control substance.

"On day 21 of gestation, the females were killed by decapitation and the uterine contents were examined. The individual fatuses were weighed, measured for crown-rump length, sexed, and examined for externally visible malformations. One-half to two-thirds of each litter was preserved in Eouin's fluid for internal examination by the Wilson method of free-hand razor-blade sectioning, and the balance of each litter was preserved in ethanol for clearing and skeletal staining with alizarin red. The internal organs of the maternal rats were examined grossly, and the brain, heart, lungs, liver, spleen, kidneys, adrenals, and ovaries were weighed and then preserved in 10% formalin for histopathological examination."

Results:

No teratogenicity or other adverse effect on fetal development was observed.

No treatment-related changes were observed in maternal tissue. Neither presence or lack of toxicity signs were reported. The authors stated that because of the high doses used and negative results, they plan no further testing.

Conclusions

'Napthalene was not teratogenic or fetotoxic in rats at the high dose level used (i.e., the MTD of pregnant rats, 395 mg/kg). As signs were not reported, neither maternal LEL or NOEL was demonstrated.

Core classification - minimum.

Study Type: Salmonella microsome test

Accession Number: 249909 (15)

Title: Detection of carcinogens as mutagens in Salmonella/microsome

test: Assay of 300 chemicals.

Journal: Proc. Nat. Acad. Sci. USA

Vol. 72, No. 12, pp. 5135-5139, December 1975

Medical Sciences

Author: Joyce McCann, Edmund Choi, Edith Yamasaki, and Bruce

N. Ames

Test Material: naphthalene

Authors' Abstract:

"About 300 carcinogens and non-carcinogens of a wide variety of chemical types have been tested for nutagenicity in the simple Salionella/microsome test. The test uses bacteria as sensitive indicators for DNA damage, and mammalian liver extracts for metabolic conversion of carcinogens to their active mutagenic forms. Ouantitative mutagenicity data from linear dose-response curves are presented: potency varies over a 108-fold range. There is a high correlation between carcinogenicity and mutagenicity: 90% (156/174) of carcinogens are mutagenic in the test and despite the severe limitations inherent in defining non-carcinogenicity, few "non-carcinogens" show any degree of mutagenicity. The results also demonstrate the great utility, and define the limitations, of the test in detecting environmental carcinogens."

Conclusions:

Secondary source. Survey only. Oualitative data. Unacceptable for regulatory purposes.

Study Type: Mutagenicity testing using S. typhimurium

Accession Number: 249909 (16)

Title: Mutagenicity of 1,2 Ring-Fused Acenaphthenes

Against S. typhimurium TA1537 and TA1538: Secreture-

Activity Relationships

Journal: Mutation Research, 78(1980) 121-135

Author: D. Gatehouse

Test Material: naphthalene

Authors' Summary:

"A number of 1,2-ring fused acenaphthenes, together with the parent compounds acenaphthene and acenaphthylene, were evaluated for mutagenicity, using the Pour-Plate Technique with <u>S. typhimurium</u> strains TA1538 and TA1537."

<u>Conclusions</u>: Inadequate protocol. Unacceptable for regulatory purposes.

Study Type: A prophage induction test in Escherica coli.

Accession Number: 249909 (18)

Title: Screening of Carcinogens with the Prophage λci ts857

Induction Test

Journal: Cancer Research, 41, 532-536, Feburary 1981

Author: Yuk L. Ho and Shiu K. Ho

Test Material: naphthalene

Conclusions: This report is unacceptable. No data were

presented.

Study Type: Salmonella histidine reversion assay

Accession Number: 249909 (19)

<u>Title:</u> Effect of Weak-, Non-, and Co-Carcinogenic Chemicals on 2-acetylaminofluorene-induced mutation in Salmonella

Journal: Toxicology, 14 (1979), 255-262 Elsevier/North Hollard Scientific Publishers, Ltd.

Author: C.E. Weeks, T.K. Rao, J.A. Young, T.J. Slaga and J.L. Epler

Test Material: naphthalene

Conclusions: Unacceptable. Inadequate protocol and data.

Study Type: Mouse mammary gland transformation in vivo

Accession Number: 249909 (20)

Title: Transformation of Cultured Mouse Mammary Glands by Aromatic Amine and Amides and Their Derivatives.

Journal: Cancer Research 39:1784-1792, May 19

Author: Quentin, J. Tonelli, R. Phillip Custer, and Sam Sorof

Test Material: naphthalene

Conclusions: Unacceptable. Inadequate protocol and data.

Study Type: Cell transformation assay in vitro

Accession Number: 249909 (21)

Title: Evaluation of an <u>In Vitro</u> Assay System for Carcinogens
Based on Prior Infection of Rodent Cells with Nontransforming RNA Tumor Virus

Journal: J. Natl. Cancer Inst., 52:1167-1173, 1974

Author: Johng S. Rhim, Dai K. Park, Elizabeth K. Weisburger, and John H. Weisburger

Test Material: naphthalene

Authors' Summary:

"Different types of chemical carcinogens (polycyclic hydrocarbons, azo dyes, aromatic amines, nitrosamines, and urethans) some noncarcinogenic analogs were tested in vitro for their transforming activity in the AKR leukemia virusinfected NIH Swiss mouse-embryo cell system. Their transforming activities in vitro were compared to their known in vivo carcinogenic activities; in general, these activities were found to be the same in vitro and in vivo."

Conclusions: Inadequate data. Unacceptable.

Study Type: In Vitro cell transformation

Accession Number: 249909 (22)

Title: Transformation of Cell Cultures as an Indication of the Carcinogenic Potential of Chemicals

Journal: J. Natl. Cancer Inst., 51:799-808, 1973

Author: Aaron E. Freeman, Elizabeth K. Weisburger, John H. Weisburger, Ronald G. Wolford, Jean M. Maryak, and Robert J. Huebner

Test Material: naphthalene

Authors' Summary:

"Over 30 polycyclic hydrocarbons, azo dyes, aromatic amines, and miscellaneous chemicals were tested to see if in vitro transformation of high-passage rat embryo cultures correlated with the known carcinogenic activity of the same chemicals in animals. In general, in vitro cell transformation was induced by the known carcinogens, but not by noncarcinogenic analogues. Certain exceptions were found."

Conclusions: Inadequate data protocols and data. Unacceptable for regulatory purposes.

Study Type: Search for correlation between naphthaleneinduced cataracts and biochemical parameters.

Accession Number: 249909 (28)

Title: A study of correlations between the biochemical and intra-ocular changes induced in rabbits by administration of naphthalene.

Journal: The British Journal of Ophthalmology, November 1930, pages 545-575.

Author: Adams, Dorthy R.

Expermental: Following naphthalene administration, certain biochemical changes in blood were observed and correlations sought between them and intraocular changes which were observed in the same rabbits. The blood parameters monitored were sugar, cholesterol, and calcium. Dose levels were in the 1 gm/kg range. Treatment times were 50 days or less.

Results: Some correlation was found between cateract formation and naphthalene-induced lowered blood calcium level. The significance of the correlation was not determined.

Conclusion: Invalid for regulatory purposes.

Study Type: Eye changes due to napthalene. Human case studies and in rabbits.

Accession Number: 249909 (30)

<u>Title:</u> Alterazioni Oculari Da Naftalina, Ricerche cliniche e sperimentali (Eye changes due to napthalene, clinical and experimental studies)

Journal: Medicina del Lavoro, 47(10):533-538, 1956

Authors: G. Ghetti and L. Mariani

Test Materia: naphthalene

Protocol:

Two types of studies were reported, (1) results from clinical examination of 21 workers employed in an obsolete plant producing dye intermediates (exposure was excessive compared to modern facilities) and (2) experimental data from exposed rabbits:

Five rabbits were treated with 1 gm/kg/day for 2 days, then with 1/2 gm/kg/day until opacification of crystalline lens occurred (23.5 grams total).

One rabbit was treated subcutaneously, 5 cc of 10% oily naphthalene solution per day (as 2 doses daily of 2.5 cc each) for 50 days.

Two rabbits were treated by topical application to the conjunctiva. A 10% oily solution was applied at the rate of 3 drops 4 times per day for 50 days.

Results:

Only two case histories were presented. The authors' summary of data follows:

The age distribution of the cases studied, although not showing a statistical correlation between the frequency of the crystalline opacity and age of the patients, has demonstrated that 2 of the 4 workers aged 20 to 30 years had opacities, as compared to 3 of 5 in the 30 to 40 age group, 2 of 8 in the 40 to 50 year age group and only 1 in the 50 to 60 year age group. The occurrence of senile lesions of the crystalline lens was greatest in the youngest age group.

Of the 5 rabbits treated orally, 2 died on the second day before the doses were reduced. Three lived until the end of the experiment.

"The dose of napthalene found to induce such alterations amounted to a total of 23.5 g given at the rate of 0.5 g/kg per day. As compared to controls, the treated animals presented signs of deteriorating general condition during the first week of treatment. There was no evidence of body weight gain."

No harm to the eyes was noted in the one rabbit treated subcutaneously.

"The animals showed a tendency to lose weight and there was limited keratosis at the injection sites."

The general condition of the two rabbits in the group . treated topically to the eyes was just about the same as in the control group. "One animal had limited keratosis of the upper palpebral edge."

Conclusions:

Damage to the crystalline lens was shown in the clinical study and in the rabbits treated orally. This report is supplemental only.

Study Type: Napthalene inhalation by infants, case studies

Accession Number: 249909 (33)

Title: Acute hemolysis due to naphthalene inhalation

Journal: The Journal of Pediatrics

Timos Valaes, M.D., D.C.H., Spyros A. Doxiadis, M.D. and Phaedon Fessas, M.D. Authors:

Test Material: Naphthalene

Author's summary:

*Acute hemolysis following naphthalene inhalation is described in 21 Greek newborn infants--16 were males and 5 females.

Severe jaundice, anemia in some and methemog.obinemia and hemoglobinuria in 2 were the main clinical manifestations. Kernicterus developed in 8 infants.

The presence of Heinz bodies and fragmentation of the red cells were prominent features in most of the cases.

A deficiency of the red cell enzyme glucose-6-phosphate dehydrogenase was detected in 12 of the infants. In the remaining 9 infants the activity of this enzyme was found to be normal."

Results:

Table 1 gives most of the relevant clinical and laboratory data.

"Table I

 .		i			Age on	Serum
1 1	•	Date of	Ėxt	oosure to naphthalene	admission	bilirubin
Case	Sex	birth	Day of life		(days)	(mg/100 ml_)
10000					. ,	-
1	М	29/5/1959	7-8	Blanket	9	14.0 -
2	М	3/10/1959	7	Clothes in baby's room	10	43.2
	M	21/9/1961	36-39	Blanket	42	5.3
3 4	M	28/11/1961	6-9	Blanket	9	55.0
5	M	26/11/1962	9	Infant's clothes	10	24.4
6	M	14/12/1862	7	Diapers	10	12.8
6 7	M	5/12/1959	7-13	Infant's clothes	13	16.5
8	M	02/09/1960	10-17	Blankets in mother's bed	18 .	20.2 ·
9	M	26/09/1961	14	Clothes in infant's room	18	17.Q
10	F	29/10/1961	5-12	Clothes in infant's room	12	28.8
11	F	08/10/1962	13	Clothes and carpet on corri-	- 14	28.0
				dor outside infant's room		
12	F	02/12/1962	7	Clothes in infant's room	8	24.0
13	F	06/03/1963	2-8	Blankets and clothes in	8	29.4
				infant's room		
14	M	17/2/1960	0-3	Blanket	.3	37.7
15	M	25/06/1961	1-5	Infant's clothes	5	28.5
16	M	05/09/1961	1-4	Sheets in mother's bed	4	46.0
17	M	30/09/1961	0-1	Blankets	3	20.2
18	М	29/12/1961	-0-4	Infant's clothes	4	38.6
19	М	25/7/1962	0-3	Sheets in infant's cot	3	41.6
20	M	5/10/1961	1-6	Blanket	6	40.9
21	M	11/3/1963	6	Infant's clothes	6	34.0

Most of the cases were seen during the autumn and winter months. This is explained by the fact that the source of naphthalene, in most cases, was a blanket or woolen clothes kept with naphthalene mothballs during the summer."

Comments:

This is supplemental information which should be considered relative to labeling.

Study Type: Enzyme inhibition by napthalene in mice lungs.

Accession Number: 249909 (34)

Title: Clara Cell Damage and Inhibition of Pulmonary Mixed-Function. Oxidase Activity by Naphthalene.

Journal: Biochemical and Biophysical Research Communications. Vol. 100, No. 3, 1981, June 16, 1981 pages 944-950.

Authors: Samuel S. Tong, Yoichiro Hirokata, Michael A. Trush, Edward G. Mimnaugh, Erika Ginsburg, Michael C. Lowe and Theodore E. Gram.

Author's Summary.

"The administration of naphthalene has been shown previously to elicit selective damage and necrosis of the Clara cells of mouse lung. Under identical conditions, we have found naphthalene administration to produce selective depression of pulmonary monooxygenase activities without accompanying changes in hepatic monooxygenases. Similarly, morphologic studies revealed dose-dependent alterations of Clara cells lining pulmonary bronchioles but no remarkable changes in livers of the same animals. The underlying biochemical basis for these organ-specific effects of naphthalene is presently obscure."

Conclusion: Supplementary.

Study Type: Bronchiolar lesions from I.P. injection in mice.

Accession Number: 249909 (35)

Title: Morphology of a Naphthalene-Induced Bronchiolar Lesion

Journal: Am. J. Pathol. 86:559-572, 1977

Authors: David Mahvi, Harvey Bank, Ph.D., and Russell Harley, M.D.

Protocol:

Young mice (15-20 gm) were in injected i.p. with .05, 1.3, 2.0 m. mol/kg naphthalene in corn oil. The mice were killed after 10 minutes, 1, 6, 12, 24, 48 hours or 7 days. Three animals per dose group were examined at each time interval. Equal numbers of untreated controls and corn oil treated controls were also examined. Trachea, lung, and heart were prepared and examined by light and electron microscope.

Results:

At 1.0 and 2.0 m. mol. groups developed dose related lesions. There was swelling and exfoliation of non-cilliated (Clara) cells and loss of cillia from cilliated cells of the bronchioles. Only minor changes in bronchiolar epithelium in the 0.05 m. mol. groups. Mice injected with corn oil did not show differences from untreated controls. One m. mol treated mouse returned to normal appearance by 48 hours. By day 7, broncheoles of all treated mice were indistinguishable by light microscopy from control groups.

Conclusions:

Dose related effects on Clara cells followed by repair, within 7 days, resulted from i.p. injections of 0.05 to 2.0 m. moles/kg in mice (6.4 to 256 gm/kg).

This is supplemental information.

Study Type: Laryngeal cancer in humans, a case studies report.

Accession Number: 249909 (36)

Title: Carcinoma of the Larynx among Naphthalene Cleaners.

Journal: Zeitschrift fur die gesamte Hygiene and ihre Grenzgebiete (Periodical for general hygiene and its frontiers)

No. 24 (1978) Installment 10.

Author: O. Wolf

Author's Summary.

"The development of cancer of the larynx has primarily exogenous causes, yet the number of reported cases of BK-31 (job-related cancer of the air passages) is minimal. This report concerns 4 laryngeal carcinomas occurring in a group of only 15 naphthalene cleaners. This is a significantly high incidence. Chronic mucous membrane irritation, the effects of heat, coal tar fumes and cigarette smoke can be considered syncarcinogenics."

Conclusions:

Naphthalene was one of several agents which may have caused cancer. Results are not definitive. Only supplementary.

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Study Type: Fetotoxic effect, human case study

Accession Number: 249909 (37)

Title: Transplancental naphthalene poisoning

Journal: Unknown

Author: John A. Anziulewicz, Herman J. Dick, M.D., and

Eugene E. Chiarulli, M.D., Syracuse, N.Y.

Nature of the case study:

The diagnosis of hemolytic anemia in a newborn infant secondary to maternal ingestion of moth balls was reported. The acute hemolytic anemia apparently originated in utero due to transplacental migration of naphthalene and/or its oxidation products. This diagnosis was supported by the case history.

Results:

"The results of the blood analyses along with normal values are presented in Table I. Direct and indirect Coombs tests were negative. The patient was given a transfusion of 1,000 c.c. of blood, and 4 days later had a spontaneous delivery of a full-term male infant, weighing 6 pounds, 3 ounces.

TABLE I

		,	era ceres amas academica	·	,	
	Normal					1
	Woman,	Mother,				!
	Ninth	Ninth	Normal	Infant,	Infant,	
	Month of	Month	Infant,	First Day	Third Day	Infant,
	Pregnancy	o£	First Day	Post	Post	First Week
	(Albritton)	Pregnancy	(Albritton)	Partum	Partum	(Albritton)
Hemoglobin						j
(Gm./100 ml.)	10.8-14.4	5.2	17.7-26.5	13.0	13.5	16.2-25.5
R.B.C.						j
(million/mm. ³)	3.7-5.0	1.70	4.7-7.0	3.56	4.39	4.5-6.4
W.B.C.]
(thousand/mm.3)	5.5-15.5	15.0	0.4-34.0	13.1	18.8	5.0-21.0
Neutrophils (%)	69	74 .	5.0-21.0	47	42	1.5-10.0
Stab forms (%)		11	1.75	8	8	.0.83
Lymphocytes (%)	25.5	0	2.0-11.5	37	46	2.0-17.0
Monocytes (%)	4.0	5	0.20-11.5	5 3	1 2	0.30-2.71
Eosinophils (%)	1.5	1	0.05-1.00	3	2	0.07-1.10
Basophils (%)	0.2	0	0.03	0	1	0:025
Nucleated red Cells		1			l	i
/100 white cells		4		35	3	
Coombs test			•			2/2/
(direct)		Negative		Negative	Negative	
Coombs test] -		1	ì -	1. 8
(indirect)		Negative		Negative	Negative	
Jaundice		Negative		Negative	Negative	

Initial hematological studies on the infant along with the normal hematological values of Albritton are also presented in Table I. Direct and indirect Coombs tests on the infant were negative. By the third day post partum, the child was noticeably jaundiced, lethargic, and anorexic. At this time hematological studies were also made (Table I). Moderate anisocytosis, poikilocytosis, and fragmentation of red cells were seen.

On being questioned further, the mother admitted having 'sucked on moth balls' during the last trimester of her pregnancy."

Conclusions:

Transplacental poisoning of the fetus is indicated. This case does not support any estimation of LEL or NOEL.

Core Classification:

Supplemental

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